Withdrawal from cocaine self-administration alters the transcriptional profile of cocaine across six brain regions

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Drug addiction is a syndrome characterized by high levels of drug consumption, difficulty abstaining from drug use, and periods of abstinence and relapse. While a great deal of work has aimed to determine the neural mechanisms of this complex and devastating disorder, we still lack a clear understanding of the transcriptional dysregulation that leads to widespread and long-lasting changes in reward related circuits. To this end, we combined cocaine self-administration with next generation sequencing in C57BL/6 mice to determine the transcriptional profile of cocaine action across six brain regions: ventral tegmental area (VTA), nucleus accumbens (NAc), caudate putamen (CPu), prefrontal cortex (PFC), basolateral amygdala (BLA), and ventral hippocampus (VHip). Mice self-administered either cocaine (0.5 mg/kg/inj) or saline i.v. for 10 days, after which they went through a 30-day withdrawal period. Following withdrawal mice were given an acute cocaine (10 mg/kg i.p.) or saline challenge to assess how the transcriptional profile of acute cocaine exposure was changed by cocaine self-administration and withdrawal. Differential expression analysis revealed that acute cocaine exposure resulted in the regulation of the largest number of genes in striatal regions, while very few genes were significantly regulated in the VTA. Interestingly, the transcriptional regulation induced by a single injection of cocaine in the NAc, CPu, BLA and PFC was opposite following withdrawal from cocaine self-administration. Differential expression analysis revealed that the differentially expressed genes included those involved in calcium signaling, excitability, and synaptic connectivity, suggesting that widespread cocaine-induced activation of limbic circuits is greatly changed following cocaine self-administration and withdrawal, and may contribute to the phenotypic characteristics of drug addiction. Together we have generated a uniquely large resource of gene expression data in six interconnected limbic brain regions implicated in drug addiction. Our analyses highlight the PFC, BLA, and striatum as key site of transcriptional regulation by cocaine and withdrawal.

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